COLON CANCER

GENERAL OVERVIEW, DIAGNOSTIC WORK-UP AND STAGING

GENERAL OVERVIEW

Epidemiology. CRC is a major global cancer burden; incidence in younger adults is increasing in many high-income countries.

Risk factors. Age, obesity, physical inactivity, alcohol, smoking, red/processed meat and IBD; hereditary syndromes include Lynch and FAP.

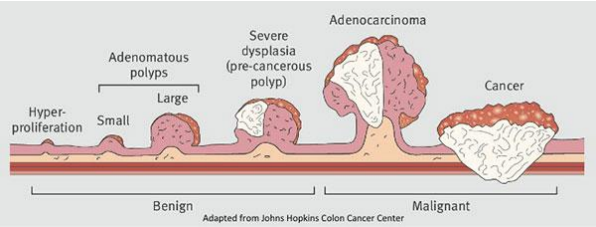
Biology. Colon cancer develops through multistep precursor lesions and shows important molecular heterogeneity by sidedness.

INITIAL WORK-UP

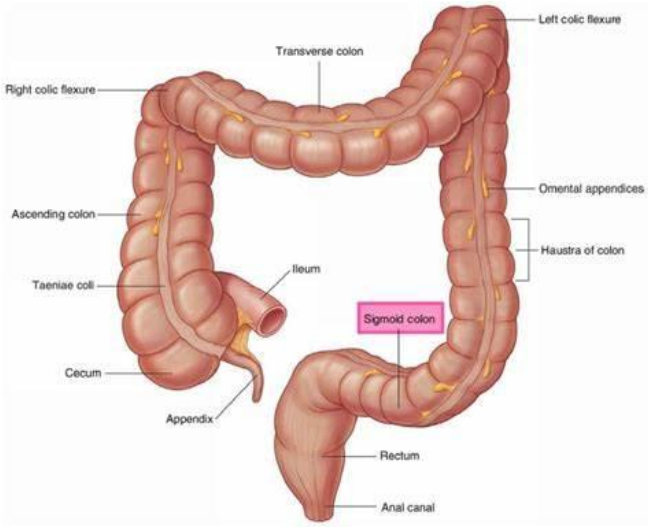
Colonoscopy. Complete colonoscopy with histology whenever feasible; complete the colon within 3–6 months after resection if preoperative examination was incomplete.

Imaging. CT thorax/abdomen; liver MRI when lesions are indeterminate or potentially resectable.

Baseline. CEA before treatment; routine PET is not required.



Adenoma–carcinoma sequence.



Colon anatomy and sidedness.

MOLECULAR AND PATHOLOGY TESTING

MMR/MSI. Test all newly diagnosed colon cancers by IHC or validated MSI assay. MLH1/PMS2 loss requires BRAF V600E and/or MLH1 promoter methylation to distinguish sporadic from Lynch-associated disease.

Metastatic disease. Test KRAS/NRAS, BRAF V600E, HER2 (3-5%, greater incidence of brain metastases) and MMR/MSI before first-line therapy; broad NGS is preferred when available.

Pathology. Report pT/pN, margins, tumour deposits, lymphovascular/perineural invasion, grade, obstruction/perforation and ≥12 examined nodes when possible.

T	N	M
T1 submucosa; T2 muscularis propria; T3 through muscularis into pericolic tissue; T4a visceral peritoneum; T4b adjacent organ/structure	N0 none; N1a 1; N1b 2–3; N1c tumour deposits without positive nodes; N2a 4–6; N2b ≥7	M0 none; M1a one distant organ/site; M1b ≥2 distant organs/sites; M1c peritoneal metastasis ± other sites

Stage	Definition	Practical implication
I	T1–2 N0	Surgery alone in most patients.
II	T3–4 N0	Adjuvant decision based on T-stage, risk factors and MMR/MSI.
III	Any T N1–2	Adjuvant oxaliplatin-based chemotherapy for most fit patients; dMMR: discuss ATOMIC data.
IV	M1	Assess resectability/ablative options and molecular profile before systemic strategy.

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LOCALIZED DISEASE — SURGERY AND ADJUVANT THERAPY

SURGERY AND STAGE II RISK

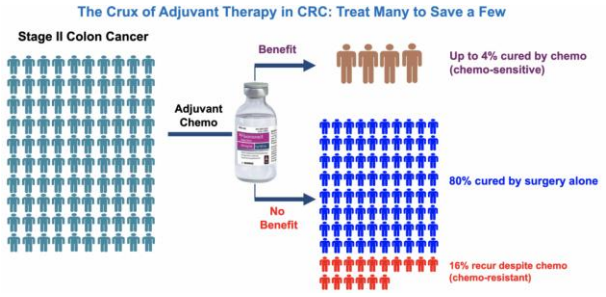
Surgery. Oncologic colectomy with adequate regional lymphadenectomy is standard for resectable disease; en-bloc multivisceral resection is preferred for adherent T4b tumours.

Early T1. Endoscopic resection can be definitive only when pathology confirms favourable features and complete excision.

Stage II high-risk. pT4 and/or <12 nodes are the strongest adverse features; obstruction/perforation, lymphovascular/perineural invasion, high grade and tumour budding add risk.

dMMR stage II. Avoid fluoropyrimidine monotherapy in low/intermediate-risk dMMR disease; individualize oxaliplatin-containing therapy for exceptional high-risk situations.

Clinical setting	Preferred approach	Duration / comments
Stage I	Observation	No adjuvant chemotherapy.
Stage II low risk	Observation	MMR/MSI mandatory.
Stage II selected high-risk	Fluoropyrimidine ± oxaliplatin	Oxaliplatin mainly for pT4 / multiple major risk factors in fit patients.
Stage III low risk (T1–3 N1)	CAPOX or FOLFOX	3 months CAPOX is a standard option; balance duration against neuropathy.
Stage III high risk (T4 and/or N2)	FOLFOX or CAPOX	Usually 6 months.



Why adjuvant therapy helps only a minority of all stage II patients.

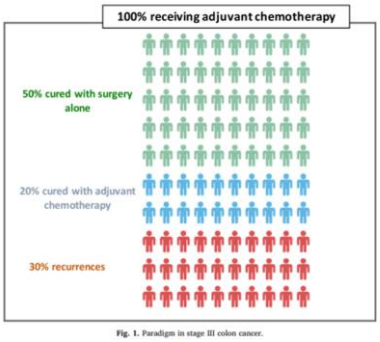


Fig. 1. Paradigm in stage III colon cancer.

Conceptual benefit of adjuvant chemotherapy.

Table 2
Summary of 3-year DFS rates according to treatment arm and risk group from the IDEA study (Grothey et al., N Engl J Med, 2018).

3 yr DFS rate (%) and HR by regimen and risk group		Regimen								
		CAPOX			FOLFOX			CAPOX/FOLFOX combined		
		3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)		HR (95% CI)
		3 m	6 m		3 m	6 m		3 m	6 m	
Risk group	Low-risk (T1-3 N1) ~60%	85.0 (83.1-86.9)	83.1 (81.1-85.2)	0.85 (0.71-1.01)	81.9 (80.2-83.6)	83.5 (81.9-85.1)	1.10 (0.96-1.26)	83.1 (81.8-84.4)	83.3 (82.1-84.6)	1.01 (0.90-1.12)
	High-risk (T4 or N2) ~40%	64.1 (61.3-67.1)	64.0 (61.2-67.0)	1.02 (0.89-1.17)	61.5 (58.9-64.1)	64.7 (62.2-67.3)	1.20 (1.07-1.35)	62.7 (60.8-64.4)	64.4 (62.6-66.4)	1.12 (1.03-1.23)
	Risk groups combined	75.9 (74.2-77.6)	74.8 (73.1-76.6)	0.95 (0.85-1.06)	73.6 (72.2-75.1)	76.0 (74.6-77.5)	1.16 (1.06-1.26)	P-value interaction test: Regimen: 0.0061 Risk group: 0.11		

Non-inferior | Not proven | Inferior

Abbreviations: 3 yr: three years; DFS: disease-free survival; CAPOX: capecitabine + oxaliplatin; FOLFOX: 5 fluorouracil + oxaliplatin.

IDEA: 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy in stage III colon cancer.

PRACTICAL ADJUVANT POINTS

IDEA. Duration is regimen- and risk-dependent: 3 months CAPOX is particularly attractive for T1–3/N1 disease; 6 months remains preferred for many T4/N2 patients.

Timing. Start once adequately recovered from surgery and avoid unnecessary delay.

DPYD. Perform guideline-concordant DPYD/DPD assessment before fluoropyrimidine therapy according to local policy.

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LOCALIZED DISEASE — 2025–2026 PRACTICE UPDATES

NEOADJUVANT CHEMOTHERAPY — pMMR/MSS

FOxTROT. Short-course preoperative oxaliplatin/fluoropyrimidine improves downstaging and disease control in radiologically staged locally advanced operable colon cancer.

NeoCol / ELECLA. Randomized studies confirm feasibility and downstaging; ELECLA did not establish a survival advantage.

UZA position. Consider selectively for convincing cT4 pMMR/MSS disease after MDT review, especially when downstaging or earlier systemic control is desirable.

NEOADJUVANT IMMUNOTHERAPY — dMMR/MSI-H

NICHE-2 / NICHE-3. Extremely high major pathological response rates with short-course neoadjuvant immunotherapy in dMMR colon cancer.

RESET-C. Alternative short checkpoint-inhibitor schedules also produce deep responses.

UZA position. Highly compelling for selected locally advanced dMMR disease, but routine use depends on access/reimbursement and MDT strategy.

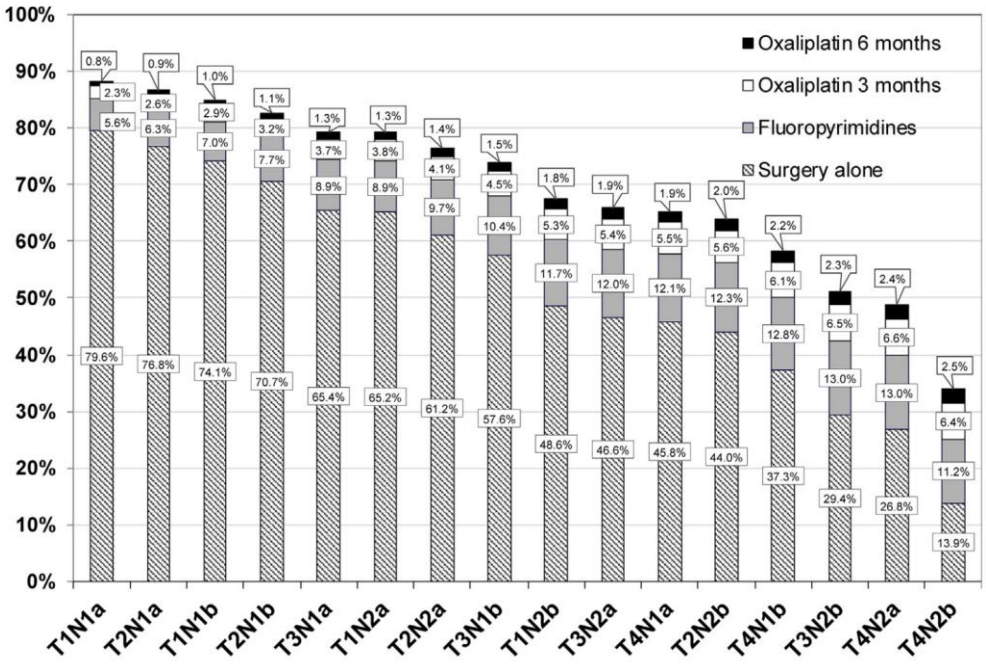
ATOMIC, ctDNA AND SURVIVORSHIP

ATOMIC. In resected stage III dMMR colon cancer, adding atezolizumab to adjuvant FOLFOX significantly improved DFS. This is an important finding, but not reimbursed, more toxicity and not sure who benefits.

ctDNA. Postoperative ctDNA is strongly prognostic. DYNAMIC supports de-escalation in stage II; randomized escalation studies have not shown that simply adding chemotherapy to ctDNA-positive patients reliably prevents recurrence.

Structured exercise. CHALLENGE showed a clinically meaningful DFS benefit from a supervised exercise programme after adjuvant chemotherapy and should be discussed as part of survivorship care.

Low-dose aspirin. ALASCCA supports aspirin 160 mg daily after curative surgery in selected PI3K-pathway altered CRC; balance bleeding risk and confirm biomarker/access strategy before use.



Stage- and subgroup-dependent absolute contribution of surgery, fluoropyrimidine and oxaliplatin to cure.

RESECTION OF METASTASES — "PSEUDO-ADJUVANT" THERAPY

Liver metastases. After complete resection, perioperative/adjuvant chemotherapy may improve DFS but has not consistently improved OS; individualize according to prior treatment and recurrence risk.

Peritoneal metastases. CAIRO6 did not establish a clear routine survival benefit for perioperative systemic chemotherapy around CRS; multidisciplinary selection remains essential.

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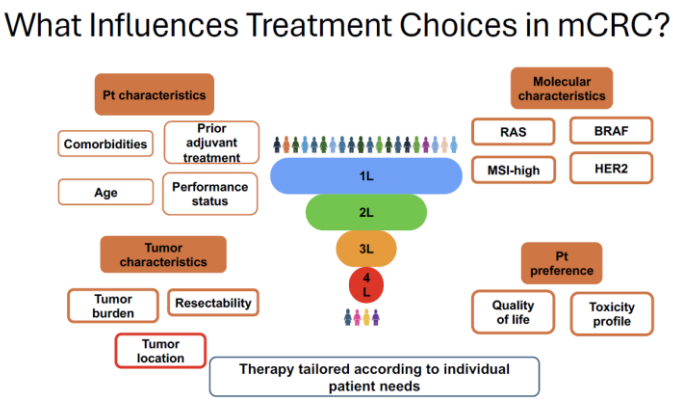
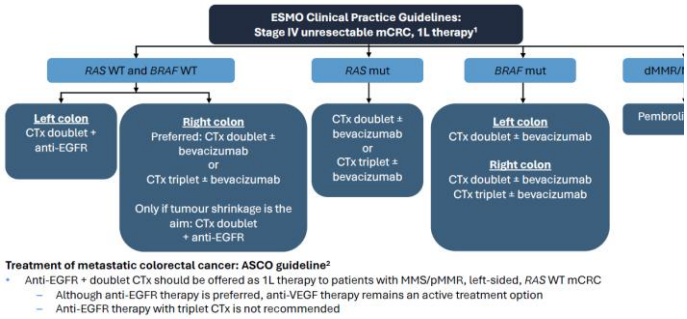
METASTATIC DISEASE — FIRST-LINE STRATEGY

BEFORE FIRST LINE

Curative intent first. Discuss potentially resectable liver/lung/peritoneal disease in an expert MDT before committing to a palliative sequence.
Required biology. MMR/MSI, KRAS/NRAS, BRAF V600E and HER2 should be available early; sidedness is critical for RAS/BRAF-WT anti-EGFR selection.
Clinical context. Performance status, comorbidity, disease burden, symptoms, organ function and patient preference determine treatment intensity.



Determinants of treatment choice in mCRC.



ESMO-style first-line algoritm

Biology / site	Preferred first-line approach	Key comment
dMMR / MSI-H	Nivolumab + ipilimumab preferred; pembrolizumab alternative	CheckMate 8HW establishes dual IO as efficacy benchmark; No reimbursement in Belgium for dual IO. Pembrolizumab reimbursed
BRAF V600E, MSS	Encorafenib + cetuximab + FOLFOX/FOLFIRI where accessible	BREAKWATER establishes targeted + chemotherapy as a preferred modern strategy; not reimbursed in first line..
RAS/BRAF WT — left-sided	Doublet chemotherapy + cetuximab or panitumumab	Anti-EGFR generally preferred first line when maximal tumour shrinkage/OS strategy is intended.
RAS/BRAF WT — right-sided	Doublet/triplet chemotherapy + bevacizumab	Anti-EGFR generally not preferred first line except selected conversion situations.
RAS-mutant	Doublet ± bevacizumab; FOLFOXIRI + bevacizumab in selected fit patients	Choose intensity according to burden, conversion goal and toxicity.

MAINTENANCE AND REASSESSMENT

Maintenance. After induction, fluoropyrimidine + bevacizumab after oxaliplatin/bevacizumab induction; fluoropyrimidine + anti-EGFR is reasonable after FOLFOX/anti-EGFR.
Reassess. Potentially convertible metastases should return to MDT during treatment, not only at baseline.

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METASTATIC DISEASE — LATER LINES, TARGETS AND OLIGOMETASTATIC THERAPY

Setting / biomarker	Preferred options	Practical note
After oxaliplatin 1L	FOLFIRI + bevacizumab / aflibercept	Select according to prior VEGF therapy, toxicity and access.
After irinotecan 1L	FOLFOX/CAPOX ± bevacizumab	Reintroduce oxaliplatin after adequate sensitivity interval.
RAS WT, anti-EGFR-naïve	Cetuximab or panitumumab-based therapy	Best positioned in earlier biologic RAS-WT settings.
BRAF V600E	Encorafenib + cetuximab	Reimbursed in Belgium since 1 jan 2026
HER2 amplified, RAS/BRAF WT	HER2-targeted therapy	Strong evidence; No reimbursement yet
KRAS G12C	KRAS G12C inhibitor + anti-EGFR	Evidence-based later-line option; No reimbursement
Refractory unselected	Trifluridine-tipiracil + bevacizumab; regorafenib; fruquintinib	SUNLIGHT supports TAS-102 + bevacizumab; fruquintinib is reimbursed in Belgium.
Prior anti-EGFR benefit	ctDNA-guided anti-EGFR rechallenge	Select only when resistant RAS/BRAF clones are absent/decayed.

LIVER / LUNG

Resection/ablation. Potentially curative in selected patients; perioperative chemotherapy may improve disease control but does not uniformly improve OS.

TransMet. Liver transplantation can be considered for highly selected permanently unresectable liver-only disease in expert programmes.

SBRT/TARE. Selective local-control tools; not a substitute for systemic therapy in diffuse disease.

PERITONEUM

CRS. Consider in selected patients when complete cytoreduction is feasible in an expert centre.

HIPEC. Oxaliplatin HIPEC did not improve OS in PRODIGE 7 and should not be routine.

EMERGING / SPECIAL MOLECULAR SUBGROUPS

POLE/POLD1. Pathogenic proofreading-domain mutations can confer marked sensitivity to immune checkpoint blockade despite MSS phenotype.

HER2. Tucatinib/trastuzumab and trastuzumab deruxtecan have meaningful activity in HER2-positive mCRC; choose according to HER2 biology, prior therapy and access.

MSS immunotherapy. Combination immunotherapy approaches remain investigational outside selected molecular contexts or trials.

FOLLOW-UP AFTER CURATIVE TREATMENT

History/CEA. Review every 3–6 months during the first 3 years, then at increasing intervals to year 5, tailored to stage and recurrence risk.

Imaging. CT-based surveillance according to recurrence risk and local protocol.

Colonoscopy. Repeat at approximately 1 year if preoperative colonoscopy was complete; if incomplete, complete within 3–6 months after surgery.

SCREENING

FIT. Organized biennial faecal immunochemical testing with high participation reduces CRC mortality.

Symptoms. Symptomatic patients require diagnostic assessment rather than screening.

Belgium/Flanders. Follow the current population-screening programme and age criteria.

WHAT'S NEW — 2025–2026

WHAT'S NEW / PRACTICE-INFORMING

Neoadjuvant dMMR. NICHE-2/3 and RESET-C reinforce the very high activity of short-course checkpoint blockade before surgery.

BRAF V600E. BREAKWATER moves encorafenib + cetuximab + chemotherapy into first-line evidence-based practice.

KRAS G12C / HER2. Targeted combinations continue to expand later-line precision treatment, but Belgian reimbursement must be checked regimen by regimen.

Liver-only disease. TransMet supports liver transplantation for exceptionally selected patients with permanently unresectable colorectal liver metastases.

Refractory MSS. Novel IO/TKI and ADC strategies remain emerging and should preferably be used in clinical trials until access and positioning are established.

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